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Cation Molecular Exchanger Based on a Conformational Hinge

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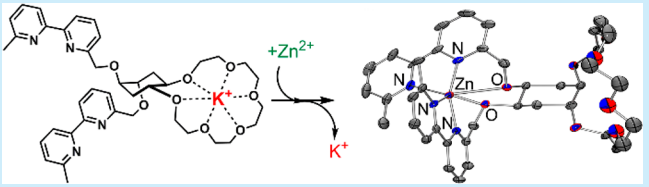
Supporting Information

ABSTRACT: A cation molecular exchanger has been developed that consists of the bipyridine and crown ether receptor subunits. It has been shown that binding of the zinc(II) cation to the bipyridine subunit induces the conformational switching of the crown ether subunits, which results in a release of the potassium cation. Two conformational states of the cation exchanger have been supported by the results from solution- and solid-state studies. It has been demonstrated that the cation exchanger is able to communicate with a cation sensor induced by a chemical stimulus.



The activity of enzymes is regulated by conformational changes induced by reversible binding of one or more guest molecules. This allosteric behavior is used by nature to transduce information on the molecular level.[1] The majority of signal outputs are small molecules and ions, which are generated in response to a recognition event. Examples are receptor enzymes or plasma membrane receptors, such as insulin receptor, β-adrenergic receptor, gated ion channels, and many others. The complexity of natural systems has raised interest among scientists to design synthetic systems that are able to process the information on the molecular level.[2,3] To date, a number of synthetic molecules and supramolecular ensembles have been developed that communicate with each other[4−7] or perform logic operations with one and more input and output functions.[8] Success has also been achieved in designing functional receptors capable of selective transport and ion exchange across the membrane.[9] However, systems that link two cation receptors sites in order to transmit the effect of binding at one site to another through a conformational hinge are unknown. To realize the idea of allosterically interacting binding sites, a certain degree of rigidity between these sites should be introduced.[10,11]

As detailed below, we have now developed a "cation molecular exchanger", which combines two recognition sites linked through a conformational hinge. The molecular exchanger releases one cation (K^+) upon coordination of another cation (Zn^{2+}). This design represents the converse of what has typically been the goal of supramolecular chemists, namely to create an allosteric system, wherein the binding of one cation increases the affinity for binding of additional cations[12,13] or anions.[14] To the best of our knowledge, this is the first metal-cation molecular exchanger with two interacting receptor sites through a cyclohexane ring, wherein binding to one site switches off the cation affinity of the other site. The reported molecular exchanger belongs to the group of receptors with homotropic negative cooperativity.[15−22] In contrast to our system, the known systems utilize metal cations together with organic cations[23] or neutral molecules.[17,19] Such types of molecular exchangers have a great potential in various applications such as sensing, ion-transport, and molecular electronics.[24,25]

Cyclohexanes are attractive molecules for the construction of molecular devices because the orientation of the axial and equatorial positions in the ring are alternated by a ring flip.[26] This property has been successfully utilized to construct a series of molecular switches. For instance, cyclohexanes have been functionalized with binding sites to recognize cations.[27,28] Synthetic receptors containing thiourea fragments have been demonstrated to bind and detect malonate, succinate[29] and maleate anions.[30] A number of switches have been developed bearing pyrene subunits for sensing applications.[29,31−33] Coordination of, e.g., Zn^{2+} induced a ring flip and, thus, effected excimer/monomer emission of the pyrene moieties.[31,32] A series of cyclohexane-based conformational switches with pH-dependent conformational equilibrium have been also reported.[34−36]

To design a cation molecular exchanger in which two receptor subunits remotely communicate with each other, we have functionalized the cyclohexane ring in positions 1, 2 and 4, 5 (Scheme 1). The substituents on the right and on the left sides have different configurations, axial and equatorial, respectively. Binding of a cation (Zn^{2+}) to two bipyridine subunits should lead to a rearrangement of a pair of substituents connected to the crown ether from equatorial (state **A**) to axial positions (state **B**) in a concerted way. As a

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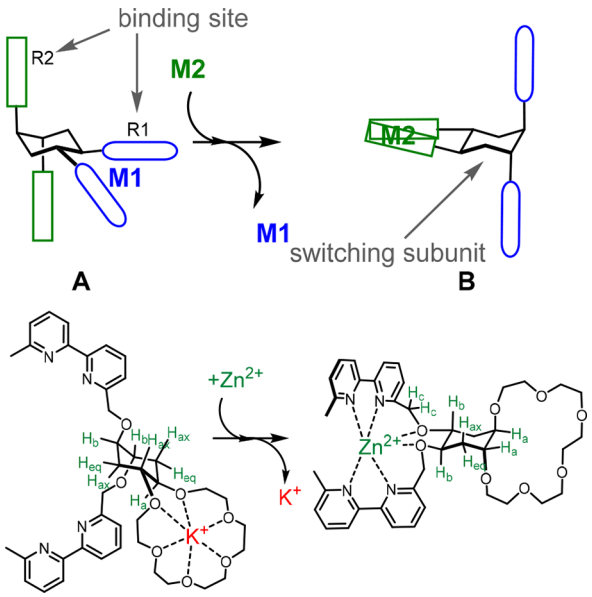
Scheme 1. General Idea for the Design of a Cation Molecular Exchanger[a]



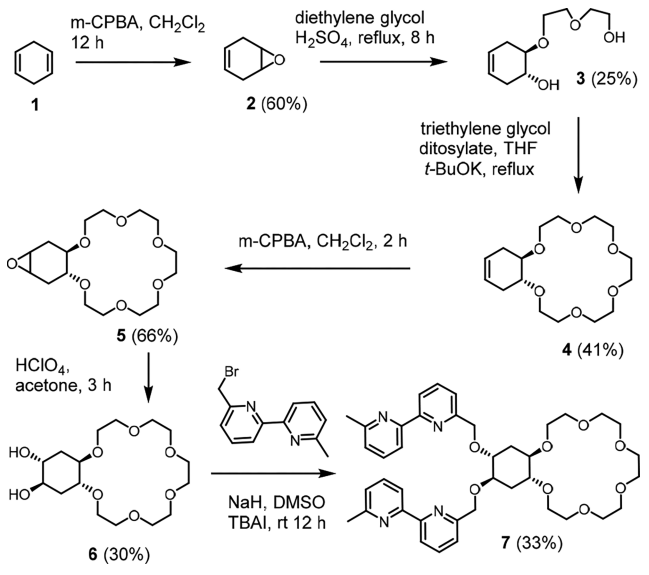
[a]Binding of cation M2 to receptor subunit R2 induces a release of the cation M1 from subunit R1. Structure of the cation exchanger and the mechanism of Zn^{2+}/K^{+} exchange.

result, the crown ether will lose the affinity for, e.g., K^{+} because of the conformational change.

The design of our cation exchanger combines 18-crown-6 and bipyridine receptor subunits capable of selective recognition of alkali (Na^{+}, K^{+}) and transition-metal cations (Zn^{2+}, Cu^{2+}), respectively. Receptor **7** was prepared as a racemic mixture by the stepwise opening of the epoxides **2**[21] and **5** obtained from 1,4-cyclohexadiene (Scheme 2). Finally, receptor **6** was alkylated with 2,2′-bipyridine subunits[37] to yield **7** in a moderate yield.

Two states of the molecular exchanger shown in Scheme 2 were successfully characterized by single-crystal X-ray analysis. The sodium complex was obtained by addition of $NaClO_4$ to

Scheme 2. Synthesis of 7



the chloroform solution of **6** (Figure 1a). The sodium ion is bound to the crown ether and coordinates the alcohol groups

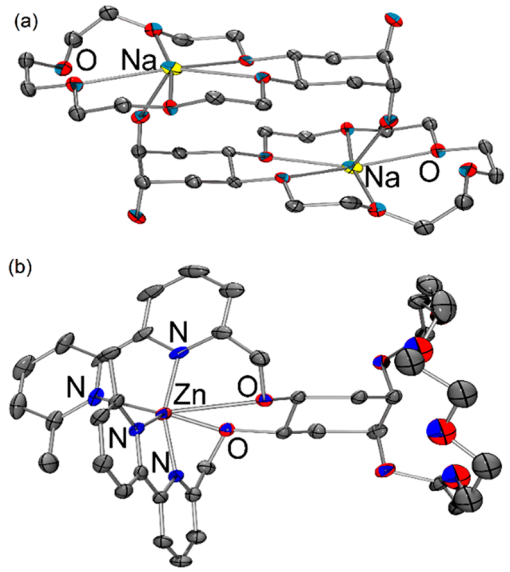


Figure 1. (a) Structure of complex **6**·$NaClO_4$ according to the single-crystal X-ray analysis showing part of the coordination network formed by the interaction between the hydroxyl group and sodium. (b) Structure of complex **7**·$Zn(ClO_4)_2$. Hydrogen atoms, perchlorate, and solvent molecules were removed for clarity.

of two other neighboring receptors. As a result, crown ether molecules form a coordination network in the crystal. Coordination of zinc(II) ion to **7** inverts the cyclohexane ring and thus elongates the crown ether subunit (Figure 1b). The crown ether loses the appropriate orientation of oxygen atoms to bind, e.g., sodium or potassium cations. Interestingly, zinc(II) coordinates two ether oxygen atoms, making the structure even more rigid.

To understand the conformation of the free receptor in solution, we conducted a series of COSY, ROESY, and temperature-dependent NMR measurements. In the COSY spectrum of free **7** we observed cross peaks H_a–H_{ax} and H_b–H_{eq}, which are indicative of equatorial positions of the ether groups belonging to the crown ether (state **A**, Scheme 1).[36] On the contrary, the COSY spectrum of the zinc(II) complex revealed cross signals H_b–H_{ax} and H_a–H_{eq} (Figures S1–S4). This fact provides evidence of the axial orientation of ether groups (state **B**). With the help of temperature-dependent NMR measurements, we determined the energy barrier ($\Delta G^{\ddagger}$, free activation energy) for switching from state **A** to state **B**, which is 7 ± 1 kcal/mol. By cooling the solution to −60 °C the distance between signals of H_{ax} and H_{eq} protons increases. The coalescence temperature was observed at −45 °C (Figure S9 and Figure 2).

Next, we investigated cation-binding properties of receptor **7** in pure methanol and in a 1:1 methanol–water mixture by using ^{1}H NMR and UV–vis spectroscopy. According to the NMR measurements in CD_3OD, **7** binds K^{+} and Na^{+} with stability constants of 3380 ± 20 and 1120 ± 10 M^{-1}, respectively. Binding of Zn^{2+} is extremely strong, so that spectra of both the complex and the receptor are observed during the NMR titration (Figure S8). Addition of K^{+} or Na^{+} cations to the zinc(II) complex of **7** does not induce any proton shifts. This fact indicates that crown ether in an

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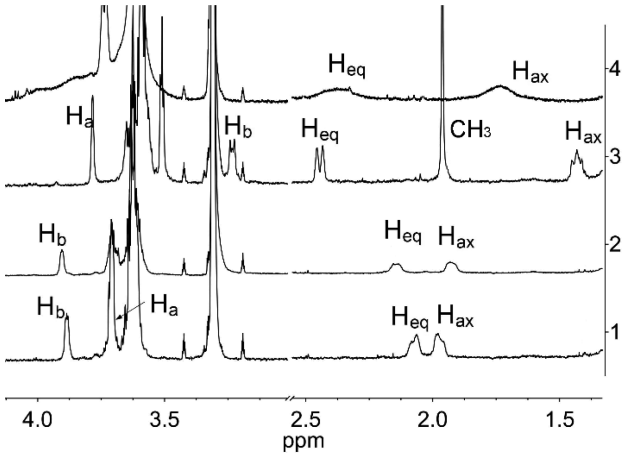

Figure 2. ^{1}H NMR spectra showing positions of the cyclohexane proton shifts (1) of free receptor **7** in CD_3OD, (2) after addition of 10 equiv of potassium salt to **7**, (3) after addition of 1 equiv of zinc(II) salt to **7**, and (4) of free receptor **7** at −60 °C.

elongated form does not bind the cations with the detectable affinity (K < 10 M^{-1}). Moreover, ^{1}H NMR spectra obtained by addition of Zn^{2+} to the receptor in the presence and in the absence of a large excess of K^+ appeared to be identical. To determine the association constant of **7** with Zn^{2+} ,we conducted UV−vis titrations in a methanol−water mixture with constant ionic strength (5 mM tetrabutylammonium perchlorate). The calculated stability constant of the corresponding complex was 2.7 × 10^7 M^{-1}, which is close to the accuracy limit of the method. Similar titration of the receptor with Zn^{2+} in the presence of 200 equiv of K^+ (as perchlorate salts) resulted in a slightly lower affinity, 1.8 × 10^7 M^{-1}. Thus, these experiments suggest that binding of the zinc(II) cation should switch the conformation of the receptor leading to a release of the bound potassium from the crown ether subunit. We also determined the stability constants of **7** with K^+ (501 ± 5 M^{-1}) and Na^+ (186 ± 3 M^{-1}) in a 1:1 methanol−water mixture, which were ca. 1 order of magnitude lower than those found in pure methanol. The complete loss of affinity of complex **7**·Zn^{2+} for potassium cation can be also explained by the repulsion between two cations with distance of ca. 9 Å. However, in systems with a similar cation distance positive cooperativity was observed, indicating that solvent strongly reduces repulsion interactions.[38,39]

To demonstrate that our cation exchanger can participate in chemical communication processes, we conducted two experiments. In the first experiment, potassium picrate was added in excess to a solution of **7** in methanol. The absorption of the picrate (340−440 nm) is well separated from the absorption of the zinc(II) complex of the receptor. Interaction between the potassium cation bound to the crown ether and the picrate anion is expected to be very strong in organic solvents.[40] Therefore, slow addition of Zn^{2+} to the potassium complex of **7** should result in a release of the potassium cation together with the picrate anion. This dissociation process should be detected by UV−vis spectroscopy. Indeed, in such an experiment, we observed an increase in the absorption of picrate up to 1 equiv of Zn^{2+} followed by a decrease of the absorption because of its interaction with the zinc(II) cation (Figure 3a).

In the second experiment, we prepared cation sensor **8**, naphthalimide-functionalized aza-15-crown-5 (Figure 3b),

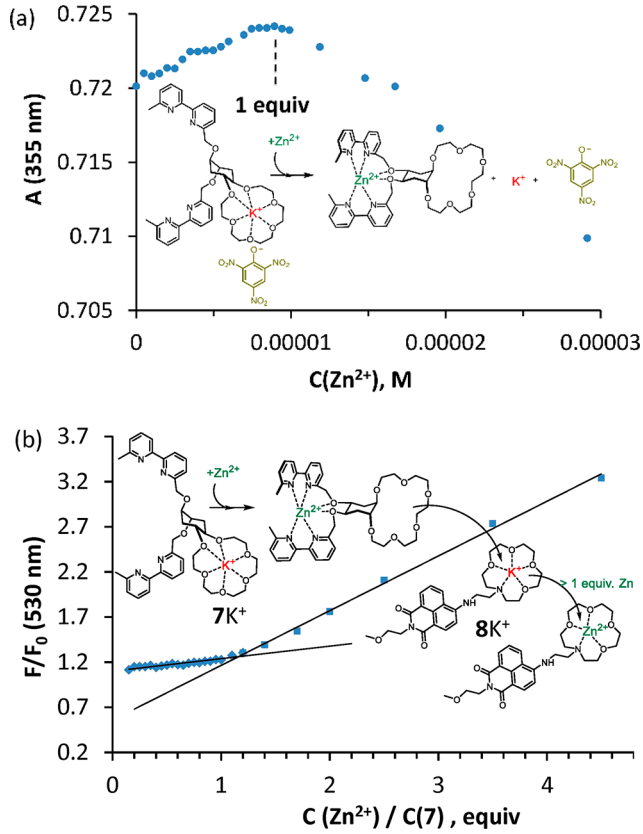

Figure 3. (a) Changes in the absorption of picrate induced by addition of zinc(II) perchlorate to a solution of **7** (0.01 mM) and potassium picrate (0.04 mM) in methanol. (b) Changes in the fluorescence spectrum of cation sensor **8** during the addition of zinc(II) perchlorate to a methanol solution **7** (0.01 mM), **8** (0.01 mM), and potassium perchlorate (0.5 mM). Conditions: ex 440 nm, em 530 nm.

which has lower affinity for potassium than receptor **7**. The absorption and emission spectra of the naphthalimide dye (ex 440 nm, em 530) does not interface with the spectra of **7** (ex 290 nm, em 340 nm). According to fluorescence titrations in methanol, receptor **8** binds K^+ and Zn^{2+} cations with a "turn-on" response and binding constants 240 ± 5 and 2950 ± 50 M^{-1}, respectively (Figures S13 and 14). Thus, in the solution containing both receptor **7** and **8**, the larger part of the potassium cations should be bound to **7**. As can be seen in Figure 3b, addition of Zn^{2+} to this solution until 1 equiv results in a small fluorescence enhancement, which is indicative of the redistribution of potassium cations between receptors **7** and **8** favoring the formation of the potassium complex with **8**. The observed fluorescence enhancement (F/F_0) is comparable with that observed for titration of free **8** with K^+. An excess of Zn^{2+} in solution leads to a much stronger fluorescence increase because Zn^{2+} replaces K^+ in crown ether **8** due to the higher stability of the zinc(II) complex.

In summary, we have demonstrated that simple conformational switching of the cyclohexane ring can be translated to a more sophisticated mechanism of controlling the binding properties of the receptors with an external chemical stimulus. The present functional molecule represents the first example of a molecular cation exchanger. We have shown that binding of the zinc(II) cation to the bipyridine receptor subunit induces the conformational switching of the crown ether subunit,

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which results in a release of the potassium cation. Two conformational states of the cation exchanger have been supported by the results from solution- and solid-state studies. Chemical signal transduction has been studied between the cation exchanger and a crown ether-based sensor. This system thus models an elementary operation of biochemical signal transduction. The present work sets the stage for inventing new type of molecular switchers that can convert one chemical signal to another one and realize chemical communication on the molecular level.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02687.

Full experimental details, NMR spectra of compounds and their complexes. UV−vis and fluorescence titrations experiments (PDF)

Accession Codes

CCDC 1854672 and 1856527 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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